Graft survival of *en bloc* versus single kidney transplantation from small pediatric donors: a meta-analysis with trial sequential analysis

Jia-Yi Zhang*, Heng-Cheng Zhang*, Chuan-Jian Suo*, Min Gu

Department of Urology, The First Affiliated Hospital of Nanjing Medical University, Nanjing 210029, China

Contributions: (I) Conception and design: M Gu; (II) Administrative support: M Gu; (III) Provision of study materials: HC Zhang; (IV) Collection and assembly of data: CJ Suo; (V) Data analysis and interpretation: JY Zhang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

*These authors contributed equally to this work.

Correspondence to: Min Gu. Department of Urology, The First Affiliated Hospital of Nanjing Medical University, Nanjing 210029, China. Email: jiangsuhpx@163.com.

Background: Although renal transplantation from small pediatric donors can relieve the pressure of the shortage of organs, the graft survival differs among different studies. We conducted this meta-analysis to evaluate the prognosis of patients receiving *en bloc* versus single allograft from small pediatric donors.

Methods: A systematic search in PubMed, Embase, and web of science was performed to identify relevant studies. Individual hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) were combined to calculate the prognostic value. A cumulative meta-analysis based on publication year was also conducted. Trial sequential analysis (TSA) was performed to estimate the quantity of the evidence.

Results: Seven studies consisting of 4,284 cases were included, and risk estimates from six of these studies were finally pooled for quantitative analysis. We found that compared with single kidney transplantation from small pediatric donors, *en bloc* kidney transplant suggested a better graft outcome of recipients (HR=0.57, 95% CI: 0.49–0.67). The findings in the current study were based on sufficient evidence by TSA. Furthermore, no evidence of publication bias in the meta-analysis was noted.

Conclusions: *En bloc* kidney transplantation from small pediatric donors was significantly associated with a superior graft survival when compared with single kidney transplant.

Keywords: kidney transplantation; small pediatric donors; graft survival; meta-analysis; trial sequential analysis (TSA)

Received: 31 May 2017; Accepted: 17 July 2017; Published: 25 August 2017.

doi: 10.21037/amj.2017.07.17

View this article at: http://dx.doi.org/10.21037/amj.2017.07.17

Introduction

Compared with the long-term dialysis treatment, the successful renal transplantation increases the opportunities of patients to survive from the end-stage renal disease (ESRD) and enables them to enjoy a better life since recovery (1,2). Within 25 years, (September 1, 1987, through December 31, 2012), the kidney transplant has saved 1,372,969 life-years (3). The number of candidates on the waiting list has nearly doubled from over 50,000 in 2002 to more than 96,000 by 2013 (4). The median waiting time for the renal transplantation of adults has grew from 3 years in 2003 to more than 4.5 years in 2009, while the donation rates have not increased (4). The prolonged waiting time for the kidney transplantation and the dialysis shares a close relationship with the significant morbidity and mortality (5). Due to the demand of donor organs over supply, the kidneys are being transplanted from donors according to the increasingly expanded criteria.

Grafts from small deceased pediatric donors are the potentially underused resources, including the single kidney or *en bloc* kidney (6). Previous researches have shown that it was technically challenging to transplant the kidneys of the small pediatric deceased donors to adults, which was associated with the vascular and urinary complications, acute rejection, delayed graft function, and the development of the hyperfiltration injury (7,8). Several studies have indicated that the *en bloc* kidney transplantation, first reported by Meakins *et al.* in 1972 (9), could avoid the size of the small anastomotic vessel and potentially limit the thrombotic complications, achieving excellent long-term graft outcomes (10-13). Consequently, the dual *en bloc* allografts from small pediatric donors have become primarily acceptable in the kidney transplantation.

In recent years, there has been growing interest in the single renal transplantation from small pediatric donors as it allows each graft to be transplanted into different recipients that increases the organ utilization (14,15). Although the single kidney transplantation enables more recipients to survive, it remains controversial on the clinical survival that some studies suggested that the superior survival outcomes (16) had been reported by others to be the inferior outcomes with an increased risk of graft failure. In addition, a few researches have directly compared the outcomes between the recipients of *en bloc* and the single kidney transplantation from the small pediatric donors (17-20). Therefore, the aim of this meta-analysis with trial sequential analysis (TSA) was to precisely evaluate the clinical significance of patients receiving *en bloc* versus single allograft from small pediatric donors, for the first time.

Methods

Search strategy

A comprehensive online search for the relevant studies (updated on Nov 1st, 2016) was performed in the PubMed, Embase, and web of science by two independent researchers (JY Zhang and HC Zhang). The MeSH search items included the keywords, including "pediatric donor", "survival", "en bloc", and "single" combined with the "kidney transplantation". In addition, the reference lists of all the identified articles, and the abstracts of the Annual Meeting of the American Society of Nephrology and the American Society of Urology were reviewed respectively. The most recent study with comprehensive data was selected while there was more than one publication focusing on the same study cohort.

Inclusion and exclusion criteria

This meta-analysis was strictly performed by the guidelines of the statement of the preferred reporting items of systematic reviews and meta-analyses (PRISMA) (21). Studies were considered eligible if they met the below criteria: (I) allografts were transplanted from 'small pediatric' donors (children younger than 10 years) to recipients; (II) both *en bloc* and single grafts were utilized for the kidney transplant; (III) the graft survival between *en bloc* and the single kidney transplantation was compared, along with a corresponding survival outcome, like the hazard ratio (HR) or Kaplan-Meier (KM) curve.

Quality assessment

The key points of the quality assessment included the following definitions: (I) the study population and country of origin; (II) the number of donors and recipients; (III) the age and weight of donors; (IV) the age and weight of recipients; (V) the assessment for outcome, and (VI) a sufficient follow-up period. Studies were considered of low-quality when they did not satisfy the above criteria to maintain the quality of the meta-analysis. In addition, the sensitivity analysis was performed to avoid bias among studies due to the certain low-quality studies.

Data extraction

Information was carefully extracted from eligible studies independently by HC Zhang and CJ Suo, per the inclusion criteria as listed above. The extracted data were reassessed by a third reviewer (M Gu). The following elements were collected from each literature: (I) the first author and the publication year; (II) patients' nationality; (III) the length of follow-up; (IV) the study size; (V) the mean age ± SD, and the mean weight ± SD of donors and recipients; (VI) the source of HRs. If HRs were not directly reported, the key data were extracted from KM plots by Engauge Digitizer V.5.1 (license type: GPL; developed by: Mark Mitchell; category: C:\Science/CAD) (22), and HRs with 95% confidence intervals (95% CIs) were then calculated by the practical methods (23). Besides, if the univariate and multivariate results were reported, only the latter ones were selected as they were adjusted for the confounding factors.

Statistical analysis

HRs and the corresponding 95% CIs of included studies were combined to compare the prognostic value of *en bloc* versus the single kidney transplantation from small pediatric donors. Besides, a cumulative meta-analysis was carried out on the basis of publication year. Heterogeneity among studies was identified by the Cochran Q test and was quantified by the Higgins I^2 statistic. The quantification of heterogeneity was assigned of low, moderate, and high to I^2 values of 25%, 50%, and 75%, respectively (24). The Galbraith plot and sensitivity analysis for individual studies were also implemented to identify the source of heterogeneity. In addition, the publication bias was estimated with the usage of Begg's test with the funnel plot. All the P values were two-sided, and a P value of less than 0.05 was considered as statistically significant. All the above-mentioned statistical analyses were performed by the Stata V.12.0 (StataCorp LP, College Station, Texas, USA), and Microsoft Excel (V.2010, Microsoft Corporation, Redmond, Washington, USA).

Trial sequential analysis

TSA was conducted for the final studies included in the meta-analysis. TSA, which was performed per the monitoring boundaries, can combine a prior sample size to evaluate the accumulating evidence (25). Our assumptions included two-sided testing with the type I error of 5%, and the type II error of 20% (power of 80%). The main results of TSA were presented in the cumulative Z-curve graph, and the monitoring boundary of required information size in the graph was determined according to the O'Brien-Fleming spending function (26). Also, the futility boundary was set on the basis of the O'Brien-Fleming -spending function. A sufficient level of evidence is reached and no further trial is needed if the cumulative Z-curve crosses the monitoring boundaries except the futility lines, otherwise the insufficient evidence is considered as a conclusion. TSA was carried out by the statistical software, and TSA version 0.9 beta (User Manual for TSA, Copenhagen Trial Unit 2011, http://www.ctu.dk/tsa).

Results

Eligible trials

A total of 49 articles were identified through the comprehensive online search. After six duplicates were removed, 43 records were screened by the title and abstract. Thirty-five studies were excluded by the preliminary review on full-text, and one study focusing on both pediatric and adult donors (age of <18 and 18–50 years) were eliminated by further detailed evaluation (27). Finally, seven studies were considered eligible for meta-analysis (16-20, 28,29). A flow diagram of the study selection process was presented in *Figure 1*. The main characteristics and data of the enrolled studies are summarized in *Table 1*. All the eligible studies were retrospectively designed, and a total of 4,284 cases from the United States were investigated. The mean age of small pediatric donors for both *en bloc* kidney transplantation and single kidney transplantation was younger than 4 years. And the length of follow-up for *en bloc* and single kidney transplantation ranged from 1.0 year to 10.0 years. The HR values were directly reported in two studies (17,18), and the HRs of the other studies were respectively extracted from the survival data or the KM curves available (16,19,20,28,29).

Quantitative synthesis results

By pooling the outcomes of seven eligible studies on a random effect model, it could be found that compared with the single kidney transplantation from small pediatric donors, the *en bloc* kidney transplantation was significantly associated with a superior graft survival (HR=0.62; 95% CI: 0.47–0.81, P<0.001) (*Figure 2*). Nonetheless, a relative moderate level of heterogeneity among studies has been observed (I^2=33.5%, P=0.172). To identify the source of heterogeneity, Galbraith plot and sensitivity analysis for the enrolled studies were performed (*Figure 3*,*4*). The value of I^2 for the secondary meta-analysis has significantly reduced to 2.6% after one study of a potential risk of heterogeneity was excluded (29). Therefore, HRs of six studies were finally pooled for the quantitative analysis, indicating a better graft prognosis for the recipients of *en bloc* kidney transplant with a HR value of 0.57 (95% CI: 0.49–0.67, P<0.001) (*Figure 5*). Per the cumulative meta-analysis based on the publication year of the six included studies, the graft survival of *en bloc* kidney transplantation was superior to that of the single kidney transplantation (HR=0.56; 95% CI: 0.47–0.67) (*Figure 6*).

TSA of the six included studies was performed by a random effect model (*Figure* 7). The heterogeneity-adjusted information size to demonstrate 43.57% of relative risk reduction (low-bias risk trial estimate) of *en bloc* kidney transplantation (with an value of 5%, and a of 20%)

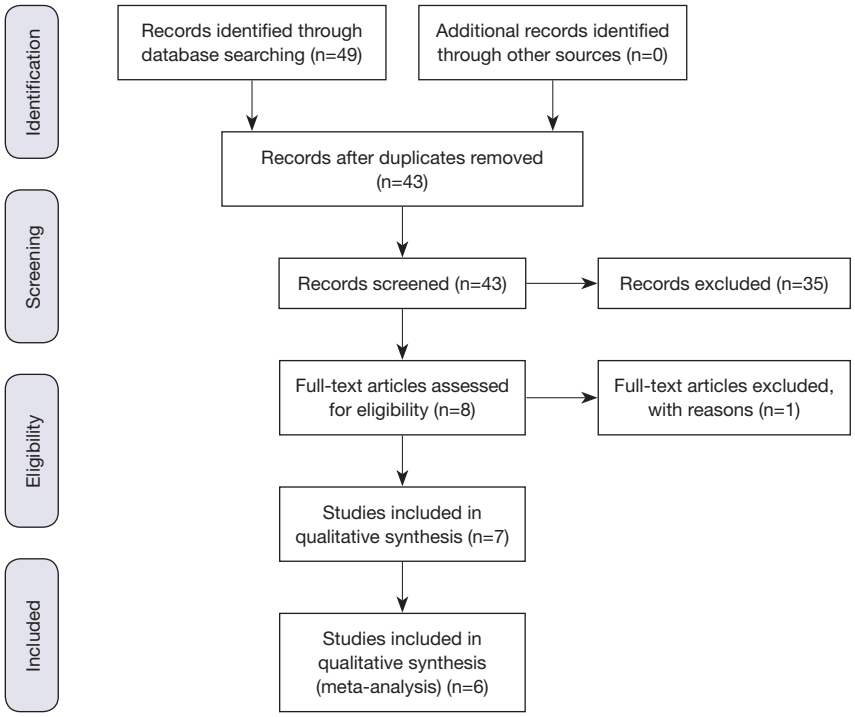

Figure 1 Flow diagram of study selection and search strategy.

was 5,493 patients. The cumulative Z-curve crossed the conventional boundary as well as the required information size (α-spending), yet not crossed the futility boundary, indicating that the clinical evidence was sufficient and no further trials were required although the number of the cases and controls has not achieved the required information size.

Publication bias

Begg's test with the funnel plot was conducted to evaluate the publication bias (*Figure 8*). As expected, the funnel plot was symmetrical and the P value of Begg's test was 0.707. Therefore, no evidence of publication bias was noted in the meta-analysis.

Discussion

Kidney transplantation can provide ESRD patients with the improved survival and growth potential, as well as elevated quality of life while compared to dialysis. Nevertheless, under the current system, the number of candidates on the waiting list will continue to increase, as each year more candidates are added than those are removed (4). Therefore, a great deal of strategies has been employed to increase the organ supply and to maximize the utilization of donor grafts. Recently, increasing evidences have reported the effectiveness of recovering and transplanting kidneys from the deceased small pediatric donors (17,18,30), indicating a potential approach to expand the donor criteria. Single kidney transplantation and *en bloc* kidney transplant are utilized from small pediatric donors into recipients although there are several unique challenges and complications, such as post-transplant vasospasm which is caused by small renal vessels, and graft failure due to the vascular thrombosis (8). Single kidney transplantation increases the utilization rate of donor organs; however, *en bloc* kidney transplant has been considered to provide a better outcome for the recipients (27).

Meta-analysis, a very effective tool in clinical and medical areas, has a stronger power than a single research as it allows a further generalization of the results obtained from the individual studies (31). There existed several advanced results for the meta-analysis. First of all, the combined sample size is larger than any single population, allowing more precision for the results in the effect estimation. Secondly, the pooled outcome has been carried out with a minimum level of heterogeneity (I^2=2.6%, P=0.400) and the Begg's test showed no publication bias (P=0.707) after the exclusion of one low-

Table 1 Main characteristics of eligible studies

First author & year	Nation	*En bloc* KT						Single KT						Source of HR
		Length of follow-up (years)	n	Donor		Recipient		Length of follow-up (years)	n	Donor		Recipient		
				Age (years)	Weight (kg)	Age (years)	Weight (kg)			Age (years)	Weight (kg)	Age (years)	Weight (kg)	
Al-Shraideh 2016	USA	7.5	34	1.4±0.8	11.0±2.6	38.0±12.1	72.2±14.7	9.6	25	3.3±1.2	17.4±3.1	45.7±16.1	75.2±12.0	Extracted
Maluf 2013	USA	1.0	815	NA	NA	NA	NA	1.0	701	NA	NA	NA	NA	Reported
Mohanka 2008	USA	1.0	19	1.0±0.8	10.0±3.0	46.0±23.0	NA	1.0	14	2.0±0.7	13.0±3.0	48.0±21.0	NA	Extracted
Pelletier 2006	USA	10.0	1,287	NA	NA	NA	66.0	10.0	1,162	NA	NA	NA	63.8	Reported
El-Sabrout 2005	USA	11.0	59	2.3±1.4	NA	46.8±14.9	NA	11.0	39	3.2±1.3	NA	42.5±15.8	NA	Extracted
Borboroglu 2004	USA	5.2	33	1.3±0.6	10.8±2.6	50.4±14.8	69.2±23.5	2.4	15	1.9±0.2	14.3±3.5	46.8±14.4	65.2±16.3	Extracted
Satterthwaite 1997	USA	5.0	22	1.25*	NA	NA	NA	5.0	59	1.3*	NA	NA	NA	Extracted

*, the youngest age available. KT, kidney transplantation; n, number; HR, hazard ratio; NA, not available.

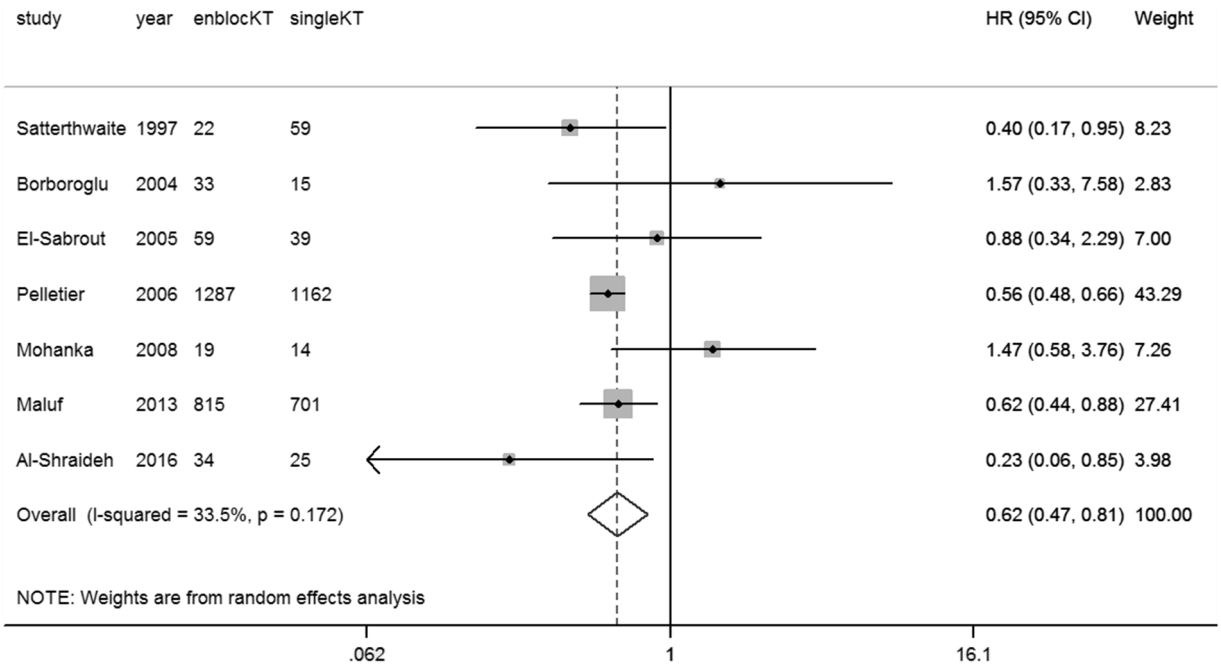

Figure 2 Forest plot of the pooled outcome of seven eligible studies on *en bloc* versus single kidney transplant. KT, kidney transplant; HR, hazard ratio; CI, confidence interval.

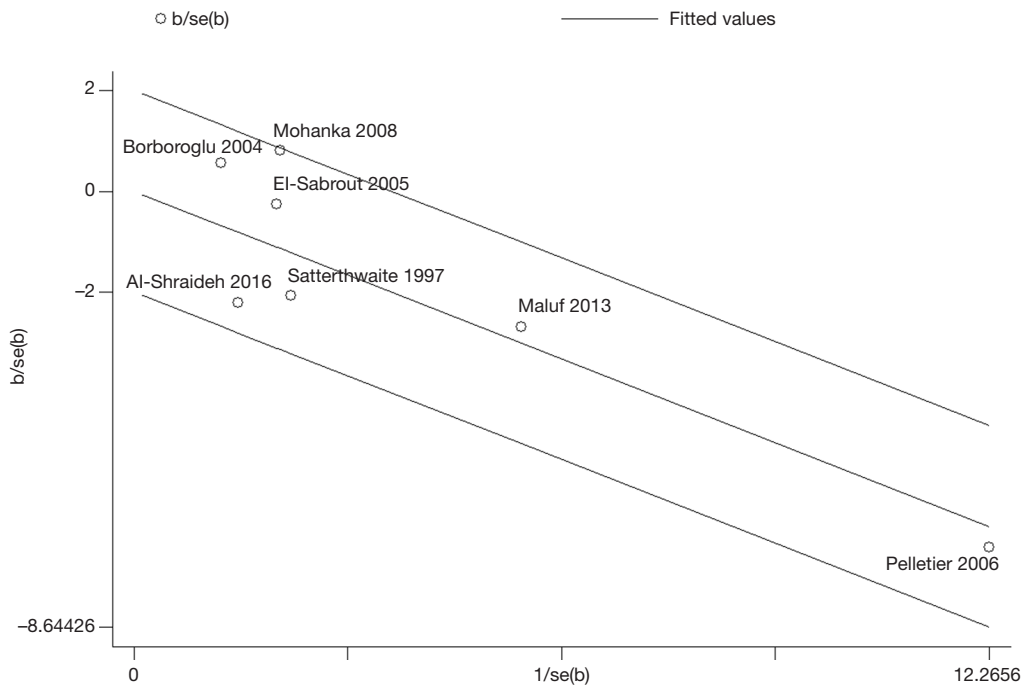

Figure 3 Galbraith plot of individual studies on graft survival of *en bloc* versus single kidney transplant.

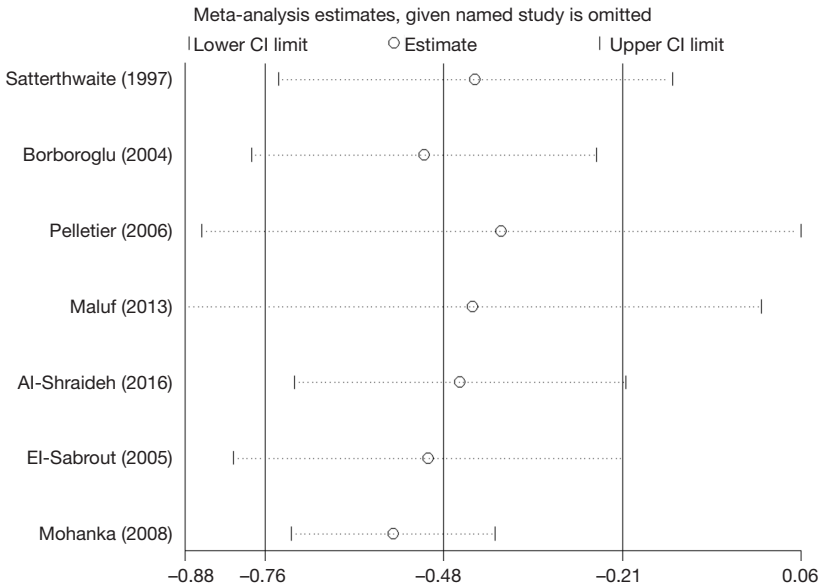

Figure 4 Sensitivity analysis for individual studies. CI, confidence interval.

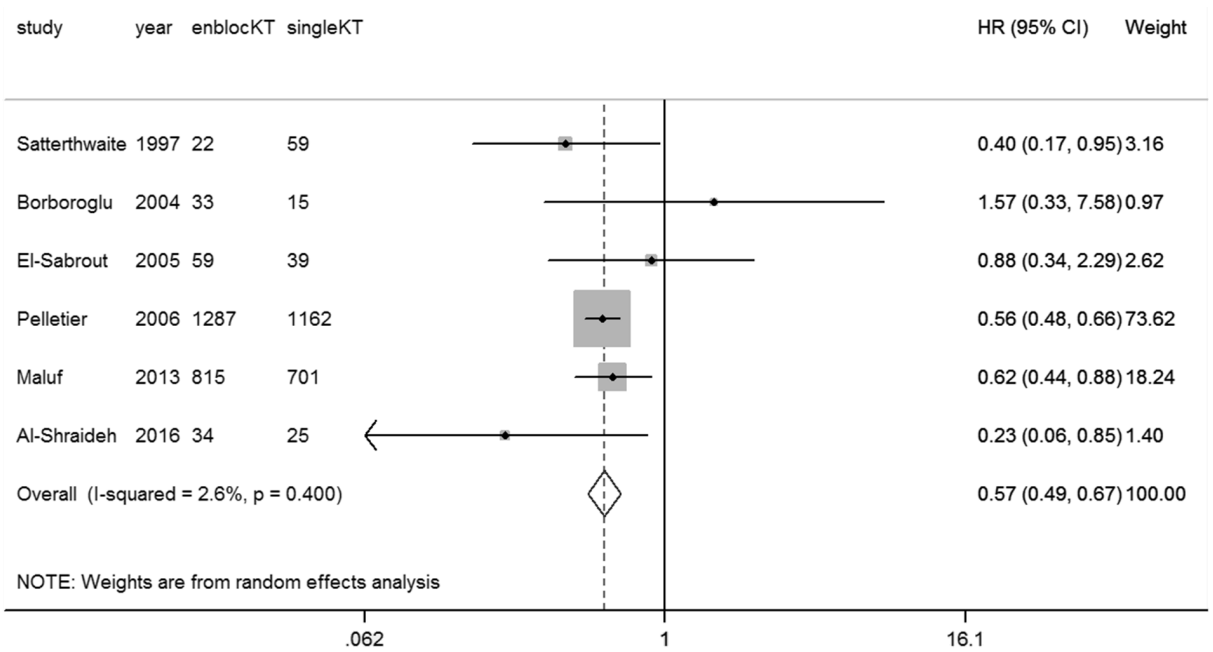

Figure 5 Forest plot of the pooled outcome of six included studies on *en bloc* versus single kidney transplant. KT, kidney transplant; HR, hazard ratio; CI, confidence interval.

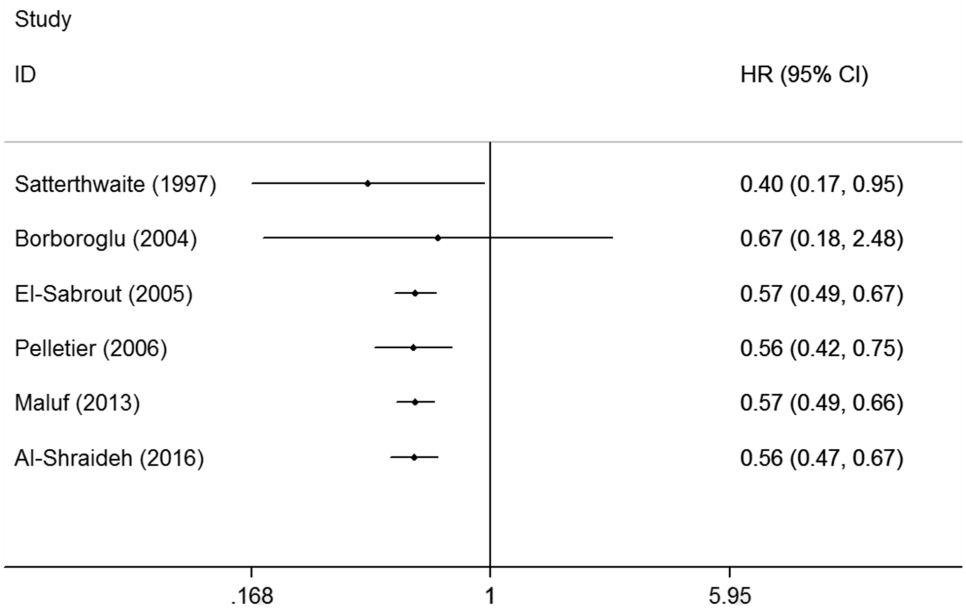

Figure 6 Cumulative meta-analysis based on the publication year of the six included studies.

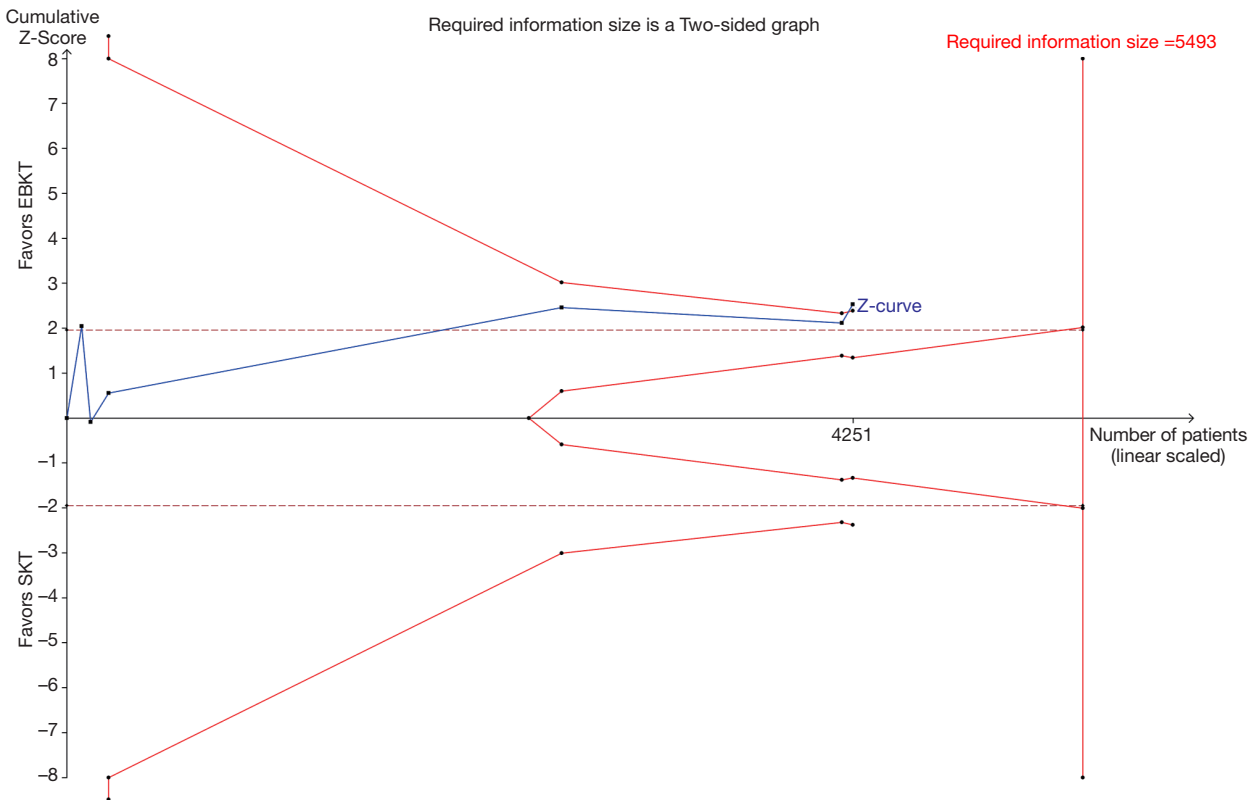

Figure 7 Trial sequential analysis of the graft outcome of six included studies on *en bloc* versus single kidney transplant. The required information size was calculated based on a two side α=5%, β=20% (power of 80%).

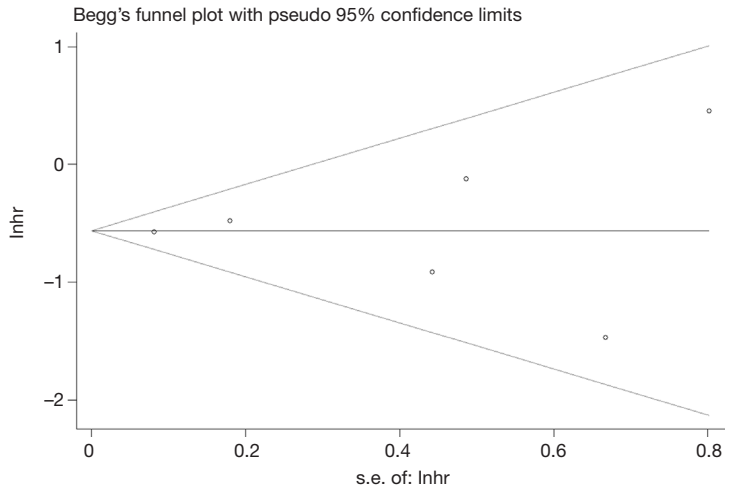

Figure 8 Begg's funnel plot used to assess publication bias.

quality study. Thirdly, our results with sufficient evidence were proved by TSA to reach a conclusion.

In the present meta-analysis, the results demonstrated that patients who received *en bloc* kidney transplantation from the small pediatric donors (mean age <4 years) were more likely to have better graft survival while compared with those who received the single renal transplant (HR=0.57; 95% CI: 0.49–0.67, P<0.001). In the TSA, the pooled sample size of the cases and controls was 4,251, which did not achieve the required information size of 5,493; nonetheless, the cumulative Z-curve has already crossed the conventional boundary and the -spending monitoring boundary, suggesting that no further trial was needed and our meta-analysis was considered to have sufficient evidence.

However, several limitations need to be further refined. First of all, the whole population included in the meta-analysis were from the United States, which might cause a risk of selection bias; thus, more populations from other countries and regions will be required in the future investigation. Secondly, a random effect model was utilized when the I^2 value for heterogeneity quantification was 2.6% among the included studies. Empirically, the random-effect model was applied if the statistically significant heterogeneity was identified (P<0.10 or I^2>50%), otherwise the fix-effect model was utilized (32). Nonetheless, a portion of recipients were found in the research by Pelletier *et al.* (17), including those who were younger than 17 years (age ranging from <2 to 17 years, 4.3% in *en bloc* kidney transplant and 9.3% in single kidney transplant), and other studies did not enroll pediatric recipients. Therefore, a random effect model was applied to minimize the residual influences caused by heterogeneity. Thirdly, the adjusted estimates could not be performed in our analysis by other covariates due to the lack of case information in certain studies. For instance, the characteristics of donors and recipients in several studies were not respectively listed according to *en bloc* or single kidney transplant, such as the average age, weight, and ethnicity (17-19). Fourthly, the follow-up period for *en bloc* and single kidney transplantation differed in various studies included, which might result in the risk of potential inaccuracy.

Conclusions

Our results indicated that compared with single renal transplant, *en bloc* kidney transplantation from small pediatric donors was significantly associated with a superior graft survival. Besides, TSA has been conducted for the first time to assess the prognosis of *en bloc* versus single kidney transplantation for recipients, and more studies by standardized unbiased methods are required to offer more detailed data of high quality.

Acknowledgements

The authors of this manuscript would like to thank the researchers of the primary studies.
Funding: None.

Footnote

Conflicts of Interest: The authors have completed the

ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/amj.2017.07.17). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Evans RW, Manninen DL, Garrison LP Jr, et al. The quality of life of patients with end-stage renal disease. N Engl J Med 1985;312:553-9.
2. Laupacis A, Keown P, Pus N, et al. A study of the quality of life and cost-utility of renal transplantation. Kidney Int 1996;50:235-42.
3. Rana A, Gruessner A, Agopian VG, et al. Survival benefit of solid-organ transplant in the United States. JAMA Surg 2015;150:252-9.
4. Matas AJ, Smith JM, Skeans MA, et al. OPTN/SRTR 2013 Annual Data Report: kidney. Am J Transplant 2015;15 Suppl 2:1-34.
5. Wolfe RA, Ashby VB, Milford EL, et al. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. N Engl J Med 1999;341:1725-30.
6. Laurence JM, Sandroussi C, Lam VW, et al. Utilization of small pediatric donor kidneys: a decision analysis. Transplantation 2011;91:1110-3.
7. Merkel FK, Matalon TA, Brunner MC, et al. Is en bloc transplantation of small pediatric kidneys into adult recipients justified? Transplant Proc 1994;26:32-3.
8. Gourlay W, Stothers L, McLoughlin MG, et al. Transplantation of pediatric cadaver kidneys into adult recipients. J Urol 1995;153:322-5 6.
9. Meakins JL, Smith EJ, Alexander JW. En bloc transplantation of both kidneys from pediatric donors into adult patients. Surgery 1972;71:72-5.
10. Merkel FK. Five and 10 year follow-up of En Bloc small pediatric kidneys in adult recipients. Transplant Proc 2001;33:1168-9.
11. Hiramoto JS, Freise CE, Randall HR, et al. Successful long-term outcomes using pediatric en bloc kidneys for transplantation. Am J Transplant 2002;2:337-42.
12. Ruff T, Reddy KS, Johnston TD, et al. Transplantation of pediatric en bloc cadaver kidneys into adult recipients: a single-center experience. Am Surg 2002;68:857-9.
13. Dharnidharka VR, Stevens G, Howard RJ. En-bloc kidney transplantation in the United states: an analysis of united network of organ sharing (UNOS) data from 1987 to 2003. Am J Transplant 2005;5:1513-7.
14. Groschl I, Wolff T, Gurke L, et al. Intermediate-term outcome of single kidney grafts from pediatric donors weighing 10-14 kg in adult recipients. Clin Transplant 2013;27:E302-7.
15. Zhao WY, Zhang L, Zhu YH, et al. Single kidneys transplanted from small pediatric donors less than 15 kilograms into pediatric recipients. Transplantation 2014;98:e97-100.
16. Borboroglu PG, Foster CE 3rd, Philosophe B, et al. Solitary renal allografts from pediatric cadaver donors less than 2 years of age transplanted into adult recipients. Transplantation 2004;77:698-702.
17. Pelletier SJ, Guidinger MK, Merion RM, et al. Recovery and utilization of deceased donor kidneys from small pediatric donors. Am J Transplant 2006;6:1646-52.
18. Maluf DG, Carrico RJ, Rosendale JD, et al. Optimizing recovery, utilization and transplantation outcomes for kidneys from small, ≤20 kg, pediatric donors. Am J Transplant 2013;13:2703-12.
19. Satterthwaite R, Aswad S, Sunga V, et al. Outcome of en bloc and single kidney transplantation from very young cadaveric donors. Transplantation 1997;63:1405-10.
20. Al-Shraideh Y, Farooq U, El-Hennawy H, et al. Single vs dual (en bloc) kidney transplants from donors ≤5 years of age: A single center experience. World J Transplant 2016;6:239-48.
21. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6:e1000097.
22. Qi X, Liu L, Wang D, et al. Hepatic resection alone versus in combination with pre- and post-operative transarterial chemoembolization for the treatment of hepatocellular carcinoma: A systematic review and meta-analysis. Oncotarget 2015;6:36838-59.

23. Tierney JF, Stewart LA, Ghersi D, et al. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials 2007;8:16.
24. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ 2003;327:557-60.
25. Thorlund K, Devereaux PJ, Wetterslev J, et al. Can trial sequential monitoring boundaries reduce spurious inferences from meta-analyses? Int J Epidemiol 2009;38:276-86.
26. O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. Biometrics 1979;35:549-56.
27. Bresnahan BA, McBride MA, Cherikh WS, et al. Risk factors for renal allograft survival from pediatric cadaver donors: an analysis of united network for organ sharing data. Transplantation 2001;72:256-61.
28. El-Sabrout R, Buch K. Outcome of renal transplants from pediatric donors <5 yr of age. Clin Transplant 2005;19:316-20.
29. Mohanka R, Basu A, Shapiro R, et al. Single versus en bloc kidney transplantation from pediatric donors less than or equal to 15 kg. Transplantation 2008;86:264-8.
30. Wang Y, Lv J, Xie W, et al. Outcome of Single Kidney Transplant From Pediatric Donors Younger Than 5 Years of Age After Cardiac Death in China: A Single Center Experience. Exp Clin Transplant 2015;13:239-42.
31. Gonzalez-Castro TB, Tovilla-Zarate CA. Meta-analysis: a tool for clinical and experimental research in psychiatry. Nord J Psychiatry 2014;68:243-50.
32. DerSimonian RF, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177-88.

doi: 10.21037/amj.2017.07.17
Cite this article as: Zhang JY, Zhang HC, Suo CJ, Gu M. Graft survival of *en bloc* versus single kidney transplantation from small pediatric donors: a meta-analysis with trial sequential analysis. AME Med J 2017;2:126.

